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(54) **Topical vaginal use of lysine p-isobutylphenylpropionate in antiinflammatory treatment.**

(57) This invention relates to the vaginal topical use of lysine p-isobutylphenylpropionate in local and targeted anti-inflammatory treatment of pathologies of obstetric and gynelogical type.

Said use is effective in the treatment of patients with inflammatory forms having either aspecific or specific etiology, and also in the treatment both of patients of medical pertinence and of patients of surgical p rtinence. The lysine p-isobutylphenylpropionate is used in the form of an aqueous solution for vaginal washes or in other pharmaceutical forms for vaginal use such as globules, suppositories etc.

EP 0 253 083 A2

investigate whether ARFEN possesses the power to resolve gynecological phlogoses. In addition to its efficiency, its systemic and local tolerance level was also evaluated. ARFEN was formulated as a vaginal wash, with an accompanying endovaginal applicator, corresponding to the following quantitative composition:

-lysine p-isobutylphenylpropionate 1.4 g
-trimethylcetylammonium p-toluenesulphonate 0.014 g
-red rose perfume 0.14 ml
-distilled water to make up to 140 ml

This composition can be varied according to requirements, both from the qualitative and quantitative aspect. For example, the composition can be varied within the following range:

-lysine p-isobutylphenylpropionate 0.5-2 g
-trimethylcetylammonium p-toluenesulphonate 0.005-0.02 g
-red rose perfume 0.05-0.2 ml
-distilled water to make up to 100 ml

For comparison purposes a placebo of the following formulation was used:

-trimethylcetylammonium p-toluenesulphonate 0.014 g
-red rose perfume 0.14 ml
-distilled water to make up to 140 ml

The patients were assigned to ARFEN or placebo treatment after randomisation in order to ensure perfect group homogeneity.

A total of 30 patients were involved in the research, their average age being 31.87 ± 8.15 years (min 19, max 58).

In addition to a group of patients of medical pertinence, a group of patients of surgical pertinence was also involved in order to investigate whether pre-post operative prophylaxis in the gynecological field was desirable.

The patients were divided into 4 groups as follows:

a) surgical group treated with placebo
b) surgical group treated with ARFEN
c) medical group treated with placebo
d) medical group treated with ARFEN

The patients of medical pertinence were treated once a day for 10 days, effecting the vaginal wash in the evening just before going to bed, in order to ensure protracted contact between the ARFEN and the vaginal mucosa for the entire night. The applications were continued for an average of 0.53 ± 1.94 days (min 6, max 10).

For the patients of surgical pertinence, the prophylaxis scheme was as follows:
-1 globule of terramycin the evening before the operation followed by the ARFEN wash in the morning one hour before the operation. These patients were in all cases treated antibiotically with curoxim at a dose of 1 g one hour before the operation, 1 g eight hours after the operation and 1 g twelve hours after the operation.

During the days following the operation, the antibiotic was administered to the extent of 1 g/day and the ARFEN wash was effected once a day.

The wash and antibiotic administration lasted an average of 9.53 ± 1.94 days (min 6, max 10).

The following parameters were checked in the patients pertaining to the two "medical groups, ie those not undergoing operation:

-irritation
-smarting
-pain
-leukorrhea

these being quantified by an arbitrary points sytem of between 0 and 3, on the following basis:

-0 = absence of symptom
-1 = symptom slight
-2 = symptom moderate
-3 = symptom intense

The four symptomatologic tests were conducted at the following times: 0 (basal), 3, 5, 7 and 10 days from the commencement of the therapy.

TABLE 1 - Case characteristics: Group a (surgical group treated with placebo)

Case No.	Age (years)	Therapy duration	Type of operation	Associated therapy	Clinical judgement
1	34	10 days	myomectomy	*	mediocre
2	33	10 days	adnexectomy sx salpingectomy dx	*	good
3	34	10 days	salpingoplasty myomectomy	*	good
4	29	6 days	ovarian cyst removal	*	mediocre
5	31	10 days	marsupialisation dx external	*	unsatisfact.
6	31	10 days	salpingoplasty	*	mediocre
7	33	10 days	salpingoplasty	*	mediocre

(*) - associated therapy for all patients who have undergone operation:
tetracyclines - cephalosporins
wash (placebo)

TABLE 2 - Case characteristics: Group b (surgical group treated with ARFEN)

Case No.	Age (years)	Therapy duration	Type of operation	Associated therapy	Clinical judgement
8	25	10 days	salpingoplasty	*	excellent
9	58	10 days	colpohysterectomy	*	excellent
10	47	10 days	vaginal hysterectomy	*	excellent
11	32	10 days	salpingoplasty	*	excellent
12	31	10 days	vulvectomy	*	excellent
13	24	10 days	metroplasty	*	excellent
14	19	10 days	ovarian cyst removal	*	excellent
15	35	10 days	salpingoplasty	*	excellent

(*) - associated therapy for all patients who have undergone operation:
tetracyclines - cephalosporins
wash (ARFEN)

Comparison at basal tim demonstrated the perfect homogeneity of the two groups, as was in fact predictable seeing that assigning of the individual treatments was made with full respect for random distribution.

TABLE 5 - Statistical results of symptomatologic parameters (M ± s.d.):
Group d (medical group treated with ARFEN)
Group c (medical group treated with placebo)

Days	0		1		5		7		10	
Group	d)	c)	d)	c)	d)	c)	d)	c)	d)	c)
Irritation	1.14±0.98	1.25±0.96	0.85±0.49	0.88±0.78	0.14±0.35	0.50±0.50	0.00	0.00	0.00	0.00
Smarting	1.85±1.24	1.50±1.00	0.57±0.49	1.25±0.96	0.29±0.45	0.87±0.95	0.14±0.35	0.25±0.43	0.28±0.45	0.12±0.33
Pain	0.71±0.69	1.00±1.11	0.42±0.49	1.00±1.11	0.42±0.49	0.87±0.78	0.00	0.12±0.33	0.00	0.00
Leukorrhea	2.42±0.49	2.37±0.69	1.85±0.63	2.00±0.70	1.29±0.70	1.75±0.66	0.70±0.70	0.87±0.78	0.42±0.72	0.50±0.78

TABLE 6 - Vaginitis: statistical results of symptomatologic parameters (M ± s.d.):
Group b (surgical group treated with ARFEN)
Group a (surgical group treated with placebo)

Days	0		1		3		5		7		10	
Group	b)	a)	b)	a)	b)	a)	b)	a)	b)	a)	b)	a)
Irritation	0.00	0.28±0.45	0.00	0.57±0.90	0.00	0.57±0.90	0.12±0.33	0.42±0.72	0.00	0.42±0.72	0.00	0.14±0.35
Smarting	0.00	0.85±0.98	2.87±0.33	2.57±0.49	1.13±0.78	2.00±0.00	0.25±0.43 *	1.71±0.45 *	0.13±0.33 *	0.85±0.34 *	0.00	0.57±0.49
Pain	0.00	0.57±1.04	2.75±0.43	2.85±0.35	0.87±0.60	2.57±0.72 *	0.25±0.43 *	1.71±0.45 *	0.12±0.33 *	1.14±0.63 *	0.00	0.85±0.63
Leukorrhea	1.75±0.83	2.00±1.07	1.50±0.70	2.57±0.49 *	0.62±0.48 *	1.85±0.33 *	0.25±0.43 *	1.14±0.63 *	0.12±0.33 *	0.85±0.63 *	0.00	0.42±0.49

* p<0.01

** p<0.001

Table 5 shows the results of the statistical analysis applied to each of the times considered. It can be observed that for each parameter, group d) treated with ARFEN showed an intensity which gradually diminished with a consequent continuous reduction in mean numerical values, such that by the 2nd check (5th day) the intensity had fallen practically to zero, making any evaluation for subsequent times impossible. The 5th day could th refore be reliably considered as the last evaluation of ach parameter. In group c), treated with placebo, complete remission of symptomatology was obs rved only on the 7th-10th day.

Table 6 also shows more rapid and intense action in the treatment of group b), treated with ARFEN, compared with group a) treated with placebo.

Claims

1. The use of lysine p-isobutylphenylpropionate for preparing aqueous vaginal wash solutions or other pharmaceutical forms for vaginal use in local and targeted anti-inflammatory treatment of pathologies of obstetric and gynelogical type.

2. The use of lysine p-isobutylphenylpropionate as claimed in claim 1, for treating patients of medical pertinence.

3. The use of lysine p-isobutylphenylpropionate as claimed in claim 1, for treating patients of surgical pertinence.

4. The use of lysine p-isobutylphenylpropionate as claimed in claim 1, for treating patients with aspecific inflammatory forms having functional organic etiology.

5. The use of lysine p-isobutylphenylpropionate as claimed in claim 1, for treating patients with specific inflammatory forms having infective etiology.

6 The use of lysine p-isobutylphenylpropionate as claimed in claim 1, wherein said aqueous solutions or other pharmaceutical forms for vaginal use are administered as first-instance medicaments while awaiting knowledge of the exact etiology of the phlogosis.

7. The use as claimed in claim 1, wherein said aqueous solutions or other pharmaceutical forms for vaginal use are administered to disinflame the anatomical structures concerned after childbirth.

8. The use as claimed in claim 1, wherein said aqueous solutions or other pharmaceutical forms for vaginal use are administered one or more times per day for 5 or more days.

9. A composition for vaginal topical use for the local and targeted anti-inflammatory treatm nt of pathologies of obstretic and gynecological type, comprising lysine p-isobutylphenylpropionate, characterised in that the lysine p-isobutylphenylpropionate is formulated in aqueous solution with the following substances and relative proportions:

lysine p-isobutylphenylpropionate 0.5 - 2.0 g
trimethylcetylammonium p-toluenesulphonate 0.005 - 0.02 g
red rose perfume 0.05 - 0.2 ml
distilled water to make up to 100.0 ml

10. A composition for vaginal topical use for the local and targeted anti-inflammatory treatment of pathologies of obstetric and gynecological type, comprising lysine p-isobutylphenylpropionate, characterised in that the lysine p-isobutylphenylpropionate is formulated in pharmaceutical forms for vaginal use such as globules, suppositories etc.

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EP 0 253 083 A3